Decline of DNA Damage and Other Biomarkers in Peripheral Blood following Smoking Cessation[1]

LaVerne A. Mooney, Regina M. Santella, Lirio Covey, Alan M. Jeffrey, William Bigbee, Mary C. Randall, Tom B. Cooper, Ruth Ottman, Wei-Yann Tsai, Laila Waznch, Alexander H. Glassman, Tie-Lan Young, and Frederica P. Perera[2]

Columbia University School of Public Health, New York, New York 10032 [L. A. M., R. M. S., M. C. R., R. O., W. Y. T., A. J., L. W., T. L. Y., F. P. P.]; New York State Psychiatric Institute, New York, New York 10032 [L. C., R. O., A. H. G., T. C.]; and Center for Environmental and Occupational Health and Toxicology, Department of Environmental and Occupational Health, Graduate School of Public Health, Pittsburgh, Pennsylvania 15238 [W. B.]

Abstract

Serial samples from 40 heavy smokers (≥1 pack/day for ≥1 year) enrolled in a smoking cessation program were assayed for cotinine, polycyclic aromatic hydrocarbon (PAH)-DNA, 4-aminobiphenyl-hemoglobin (4-ABP-Hb) adducts, and glycophorin A (GPA) mutations. Blood samples were taken while subjects were smoking, and 10 weeks and 8 and 14 months after quitting. Cotinine was used to assess compliance with the cessation protocol. A significant reduction in mean PAH-DNA and 4-ABP-Hb adducts was observed after cessation in all persons who were cotinine-verified quitters (≤25 ng/ml) for ≥8 months ($P < 0.05$). Neither the GPA N/ϕ nor the GPA N/N mutation V_f was significantly reduced after smoking cessation, but results are limited by the small number ($n = 18$) of heterozygous individuals studied.

The substantial reduction (50–75%) in PAH-DNA and 4-ABP-Hb adduct levels after quitting indicates these carcinogen adducts are reflective of smoking. Passive exposure to smoke at home was significantly associated with PAH-DNA adducts in active smokers and in ex-smokers 10 weeks after quitting ($P < 0.01$). The estimated half-life of the PAH-DNA adducts in leukocytes is 9–13 weeks by inspection of the mean biomarker levels from baseline and 10 weeks sample and 23 (95% confidence interval, 10–36 weeks) using a linear regression model that adjusted for background. Women had higher levels of 4-ABP-Hb adducts at baseline and after smoking cessation after adjustment for amount of smoking, suggesting that women may be more suseeptible to carcinogenic exposures. For 4-ABP-hemoglobin adducts, the estimated half-life is 7–9 weeks from inspection of the means, which is consistent with the lifetime of hemoglobin, as compared with 12 weeks (95% confidence interval, 10–14 weeks) using a regression model that adjusted for background. The variability in the confidence intervals for the regression half-lives illustrates that some individuals may be less efficient in eliminating genetic damage than others.

Thus, PAH-DNA and 4-ABP-Hb adducts can be useful as intermediate biomarkers in intervention programs and in identifying persons who may be at increased risk of cancer from exposure to cigarette smoke due to high levels of carcinogen binding.

Introduction

Cigarette smoke is a complex aerosol of more than 4000 chemicals, of which 43 are known carcinogens (1). Included in the toxic mixture are a variety of compounds including nicotine, 4-ABP[3] (an aromatic amine), and BaP (a PAH; Refs. 2, 3). BaP and 4-ABP, both human carcinogens, have been shown to bind covalently to cellular macromolecules *in vivo* (4–7).

BaP is generated by incomplete combustion and has been detected in cigarette smoke (400–800 ng/day for 20 cigarettes); charcoal-broiled, smoked, and grilled meats (10,000 ng/200-g steak); ambient air (9–40 ng/day); and drinking water (1 ng/day; Refs. 8, 9). Numerous previous studies have attempted to assess the effect of smoking on PAH-DNA adduct formation in total peripheral leukocytes, but the results have been inconsistent between studies. Several studies of leukocyte DNA have shown an association between PAH-DNA adduct levels and smoking measured by ELISA (10, 11). Other studies have not been able to demonstrate a statistically significant relationship between adducts and smoking by either ELISA or ^{32}P postlabeling (12–16), although higher levels have been observed in healthy smokers than in nonsmokers (16). However, recent studies have demonstrated an association between smoking and PAH adducts by ^{32}P postlabeling and ELISA using the longer-lived lymphocyte/monocyte fraction of the WBC, supporting their potential to reflect smoking-related damage (17, 18).

4-ABP is a rodent mammary carcinogen (8) and a human bladder carcinogen found in cigarette smoke, dyes, and in occupational settings (19, 20). The majority of nonoccupational human exposure results from active and passive smoking. 4-ABP-Hb adducts have been significantly correlated with recent smoking and smoking status (16, 21, 22) and have been used to measure passive exposure to cigarette smoke (23, 24).

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[2] To whom requests for reprints should be addressed, at Columbia University School of Public Health, Environmental Sciences Division, 60 Haven Avenue, B-109, New York, NY 10032.

[3] The abbreviations used are: 4-ABP, 4-aminobiphenyl; 4-ABP-Hb, 4-ABP-hemoglobin; BaP, benzo(*a*)pyrene; PAH, polycyclic aromatic hydrocarbon; V_f, variant frequency; ETS, environmental tobacco smoke; CI, confidence interval; BPDE-I, *r*-7,*t*-8-dihydroxy-*t*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene; PFPA, pentafluoropropionic anhydride.